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(54) [Title of the Invention]

Absorbing Agent for Decreasing Guanidino Compounds, Water and Potassium Ions

(57) [Summary]

[Objective]

To offer the orally administered drug which can discharge the water, the guanidino compounds accumulated in the body and the potassium ions of the hemodialysis patient to outside of the body without using hemodialysis.

[Method to Achieve the Objective]

Guanidino compound decreasing agent which includes an acrylic type water absorbent resin as the effective component.

[Scope of the Patent Application]

[Claim 1]

Guanidino compound decreasing agent characterized by the fact that it includes an acrylic type water absorbent resin as the effective component.

[Claim 2]

Guanidino compound decreasing agent and water adsorbing agent characterized by the fact that it includes an acrylic type water absorbent resin as the effective component.

[Claim 3]

Guanidino compound decreasing agent, and water and potassium ion adsorbing agent characterized by the fact that it includes an acrylic type water absorbent resin (which excludes potassium salts) as the effective component.

[Claim 4]

Reducer or adsorbent of which the effective component is an acrylic acid or a methacrylic acid alkali metal salt type polymer, as was described in any one of Claim 1 to Claim 3.

[Claim 5]

Reducer or adsorbent of which the effective component is an acrylic acid or a

methacrylic acid alkali earth metal salt type polymer, as was described in any one of Claim 1 to Claim 3.

[Claim 6]

Reducer or adsorbent in which the effective component is a self cross linking type acrylic acid metal salt type polymer, as was described in any one of Claim 1 to Claim 3.

[Claim 7]

Reducer or adsorbent in which at least a part of the metal salts are calcium salts, as was described in Claim 6.

[Detailed Explanation of the Invention]

[0001]

[Technical Field in Which this Invention Belongs]

This invention relates to the drug for reducing guanidino compounds. In particular, it relates to the drug with new action for decreasing the guanidino compounds which can reduce the guanidino compounds accumulated in the body of acute and chronic kidney patients who are receiving hemodialysis, or the patients who do not need hemodialysis yet but who's water intake is limited due to the deterioration of their kidney function when it is administered orally, and which can remove the guanidino compounds with the water accumulated in the body and which can discharge these to outside the body without hemodialysis, and also which can remove the potassium ions accumulated in the body.

[0002]

[Existing Technology]

Acrylic type water absorbent resins such as sodium poly acrylate, etc., have been used for the hygiene products such as sanitary napkins, diapers, disposable wipe cloths, etc., and also as the food additives, and farm and garden products. Also it has been known in the references that this can be utilized as the digestive ulcer treatment drug (German Patent No. 2412090), for the bleeding control and as a scratch protecting agent (Patent Kokai No. S62-70318), and as the intoxication prevention agent (Patent Kokai No. H1-153643), etc.

[0003]

On the other hand, concerning the remedy or treatment of the acute and chronic kidney patients whose kidney function is deteriorated, so that the nitrogen, metabolic wastes, water, etc., which are supposed to be discharged into urine are accumulated in the body, the kidney transplant and CAPD (continuous ambulatory peritonea dialysis), etc., have been known too, however, the number of donors is too small in the case of kidney transplants, and peritonitis tends to occur in the case of CAPD, and due to these disadvantages, presently kidney patients mostly depend on the hemodialysis.

[0004]

It is said that there are 500,000 to 600,000 kidney patients in Japan, and the Japan dialysis medical survey research committee reported that the number of chronic dialysis

patients in Japan at the end of 1994 was 143,709 persons, and that this was an increase of 9,411 persons compared with the previous year.

[0005]

These dialysis patients and the patients who do not need hemodialysis yet but who's water intake is limited due to the deterioration of their kidney function, are unable to or have a difficult time to discharge the water, etc., to outside their body due to the deterioration of their kidney function, and also the angina pectoris in dialysis patents tends to appear during the dialysis, and also attacks tend to be induced when the body fluid is increased the most before dialysis, therefore, the water intake of these patients must be strictly limited. Their allowable water intake is about 1 L per day, and in the case of dialysis patients, their allowable water intake until the next dialysis is presently restricted to 4 to 5 % of their body weight. Thus, the allowable water intake is equivalent to about half of the water intake that a healthy person intakes normally. This strict water control over a long period of time, gives psychological and physical pain to the dialysis patients, and this can be listed as one of the most important disadvantages of hemodialysis.

[0006]

The hemodialysis of the above mentioned dialysis patients requires about 3 hours in the case of, for example, removing 2 L of water and metabolic waste, etc., and it takes a longer time than that if a water volume larger than that must be removed. The patients must repeat such dialysis 2 to 3 times per week, therefore, their return to a normal life style in society is difficult presently due to this time restriction.

[0007]

Thus, the hemodialysis applied to the kidney patients presently, is an essential factor for sustaining the life of the said patients, however, it brings quite large psychological pain, and in addition, it requires long treating times, therefore, the development of new technologies that can reduce these disadvantages has been desired.

[0008]

In addition, in the renal failure patients such as dialysis patients, etc., there is another large problem of accumulating guanidino compounds such as methyl guanidine, guanidino propionic acid, guanidino butyric acid, etc., which is one of the materials that cause uremia in the body. Methyl guanidine has cell toxicity. Guanidino propionic acid has hemolytic action, and guanidino butyric acid has a central nerve system impairing action, therefore if these materials accumulate in the body, various diseases might be generated.

[0009]

Among these, the concentration of methyl guanidine in the blood stream can be reduced by hemodialysis, however, the concentration in the organs does not decrease easily even if dialysis is used. Concerning the guanidino propionic acid and guanidino butyric acid, the concentration in the blood and in the organs can almost never be decreased, even by hemodialysis.

[0010]

Thus, although hemodialysis is performed in order to remove the metabolic wastes and

toxic materials in addition to removing water, it can not sufficiently remove some of the toxic materials that are accumulated in the body, depending on the material, therefore, the development of a technology that can replace this, or that can supplement this, has been desired too.

[0011]

In addition, generally, if fever, infection or eating failures, etc., occur in the body of hemodialysis patients, cytoplasm or self protein is broken, and potassium ions move to the outside of the cells, and the potassium concentration becomes high and hyperkalemia is induced easily even though potassium is not taken orally, and it is known that sometimes the symptoms such as sensory problems in all four limbs, nausea, diarrhea, oliguria, muscle tiredness and a feeling of no strength, flaccid muscle paralysis, metabolic acidosis, respiratory muscle paralysis, dyspnea, and arrhythmia, etc., will appear. Therefore, a potassium adsorbing agent is often administered to such dialysis patients, however, already known potassium adsorbing agents are accompanied by constipation as a side effect, therefore the improvement of this is also desired.

[0012]

[Problem That this Invention Intends to Solve]

Therefore, the objective of this invention is to offer the new technology, especially to offer the orally administered drug which can discharge the water that is in- taken by a dialyses patient, the guanidino compounds and potassium ions that are accumulated in the body, to the outside of the body without hemodialysis.

[0013]

The inventors of this invention studied to achieve the above mentioned objective, and as the result, they discovered that some types of water absorbent resins that has been used for hygiene products, can decrease the guanidino compounds that are accumulated in the body when it is taken orally by the patient, and in addition, they discovered that it has the action to adsorb the water and potassium ions also and it can discharge these to outside the body, and that the dosage of oral administration required to produce the above mentioned effect is safe, and this invention was completed.

[0014]

[Method to Solve the Problem]

According to this invention, the guanidino compound decreasing agent characterized by including an acrylic type water absorbent resin as the effective component, can be offered, especially, the guanidino compound reducing agent, the water absorbing agent and the guanidino compound reducing agent, and adsorbing agent of water and potassium ions, can be offered.

[0015]

[Form of Enforcing this Invention]

A preferred example included in the above mentioned acrylic type water absorbent resins which is the effective component of the decreasing agent and adsorbing agent of this invention, can be selected from the polymers and the cross linked materials of the said polymers which include acrylic type monomers that can be indicated by the general formula,

$CH_2 = CR^1 COO R^2$

[In the formula, R^1 indicates a hydrogen atom or a methyl group, and R^2 indicates a hydrogen atom or a metal atom.]

as the essential structural unit.

[0016]

Here, the metals which can form the metal salts are alkali metals such as sodium, potassium, lithium, etc., and alkali earth metals such as calcium, magnesium, etc.

[0017]

The above mentioned preferred acrylic type water absorbent resin includes acrylic acid type polymers, acrylic acid metal salt type polymers, methacrylic acid type polymers and methacrylic acid metal salt type polymers, and these polymers may be the cross linked type too. Among these, the cross linked materials of poly acrylic acid or poly acrylic acid alkali metal salts are suitable, and further, the ones in which a part of the said cross linked material has the form of a calcium salt, are the most suitable.

[0018]

The above mentioned cross linked material includes the self cross linked material which is obtained without using any cross linking agent, and the cross linked material which is obtained by normal methods that use various cross linking agents that are commonly used.

[0019]

Multi- valent allyl compounds, multi- valent vinyl compounds, multi- valent epoxy compounds, halo epoxy compounds, multi- valent alcohols, multi- valent amines, hydroxy vinyl compound, etc., can be used as the above mentioned cross linking agent. The representative cross linking agents are listed below.

[0020]

Multi- valent allyl compounds : N, N - di- allyl acryl amide and N, N - di- allyl methacryl amide (from now on, these will be indicated as "N, N - di- allyl (meth) acryl amide"), di- allyl amine, di- allyl methacryl amine, di- allyl phthalate, di- allyl maleate, etc.

[0021]

Multi- valent vinyl compounds : Di- vinyl benzene, N, N' - methylene bis (meth) acryl amide, ethylene glycol di (meth) acrylate and poly ethylene glycol di (meth) acrylate (from now on, these will be indicates as "(poly) ethylene glycol di (meth) acrylate"), poly propylene glycol di (meth) acrylate, tri metharol? (*phonetically written, may be a typo of methylol? - Translator*) propane tri acrylate, etc.

[0022]

Multi- valent epoxy compounds : (poly) ethylene glycol di- glycidyl ether, (poly) propylene glycol di- glycidyl ether, glycerine -1, 3- di- glycidyl ether, tri methylol propane tri glycidyl ether, (poly) glycerine poly glycidyl ether, etc.

[0023]

Halo epoxy compounds : epi chloro hydrine, α - methyl chloro hydrine, etc.

[0024]

Multi- valent alcohols : (poly) glycerine, (poly) ethylene glycol, tri methylol propane, penta erythritol, etc.

[0025]

Multi- valent amines : ethylene diamine, etc.

[0026]

In addition, the above mentioned acrylic acid type polymers, acrylic acid metal salt type polymers, methacrylic acid type polymers and methacrylic acid metal salt type polymers include not only the homo polymers of acrylic acid and methacrylic acid, but also the co-polymers of these, and the co-polymers of each of these monomers and other monomers that can co-polymerize with these, or the co-polymers with the polymers that can graft polymerize with these too. These co-polymers may be random polymers, block polymers or graft polymers.

[0027]

Here, those that can be listed as other monomers that can co-polymerize with (meth) acrylic acid are for example, alkyl (meth) acrylates such as hydroxy ethyl (meth) acrylate, (methoxy) poly ethylene glycol (meth) acrylate, glycerin (meth) acrylate, glycosyl ethyl (meth) acrylate, etc.; acryl amide type compounds such as N, N - di-

methyl acryl amide, acryl amide, etc.; carboxylic acid type compounds such as maleic acid and its metal salts, itaconic acid and its metal salts, etc.; sulfonic acid type compounds such as 2- acryl amide -2-methyl propane sulfonic acid and its metal salts, vinyl sulfonic acid and its metal salts, styrene sulfonic acid and its metal salts, etc.; and N - vinyl pyrrolidone, etc.

[0028]

Also, those that can be listed as the polymers that can graft polymerize with (meth) acrylic acid are for example, the hydrophillic poly saccharides such as starch, carrageenan, agarose, carboxy methyl cellulose, etc.

[0029]

Some of the above mentioned various water absorbent resins are sold commercially, and they can be produced by ordinary methods too. General production methods that are known are for example, the method in which the monomer is polymerized in an aqueous solution of monomer (aqueous solution polymerization), the method in which the suspension liquid of an aqueous monomer solution is made in a non- aqueous organic solvent, and this is polymerized (reverse phase suspension polymerization), and the method in which the aqueous solution of the polymer is cross linked by using a cross linking agent (polymer cross linking method), etc. The water absorbent resin utilized in this invention can be made by any of these methods.

[0030]

Especially, the self cross linking type acrylic acid alkali metal salt type polymer which is

one of the suitable effective components of this invention should be preferably produced by polymerization by suspension - dispersing a high concentration aqueous solution of the acrylic acid alkali metal salt in an organic solvent (reverse phase suspension polymerization). (For example, see Patent Kokoku No. S54-30710 Official Gazette)

[0031]

Also, the self cross linked type acrylic acid metal salt type polymer in which a part of alkali metal atoms are substituted by calcium and which is one of the especially suitable effective components in this invention, can be produced, for example, by polymerizing by suspension - dispersing a high concentration aqueous solution of the acrylic acid alkali metal salt and acrylic acid calcium salt in an organic solvent, or more preferably, by slowly adding an aqueous solution of calcium chloride into the water swelled polymer of the self cross linked type acrylic acid alkali metal salt obtained by the above mentioned method, and by performing the counter ion exchange.

[0032]

Thus, the acrylic type water absorbent resin that can be utilized as the effective component of the drug for decreasing the guanidino compounds of this invention can be produced.

[0033]

The acrylic resins that are especially suitable for this invention are for example, the ones of which the physiological saline solution absorbing ability (volume (mL) of a physiological saline solution absorbed per 1 g) is 5 to 100, more preferably 15 to 70.

[0034]

Concerning the administration of the drug for reducing the guanidino compounds of this invention, the acrylic type water absorbent resin that is obtained in the above mentioned manner, can be administered orally to the patients who need to decrease the guanidino compounds and who need to absorb- remove water and potassium ions, in an ordinary form that can be obtained, for example, a powder form, a fine powder form, a bead- like form, a flake- like form, the gel form, etc. Also, the same as for ordinary orally administered agents, a general support material can be used to make it into an appropriate shape such as tablets, granules, capsules, etc., to be used.

[0035]

The dosage can be determined at any level depending on the hemodialysis patient to which it is to be administered, and depending on the amount of water that was in-taken by the patient, and the dosage is not particularly limited. For example, in the case when the decreasing agent of this invention is applied to the patient who took 700 mL of water, generally, the amount of the effective component should be in the range of 5 to 20 g per day. By this oral administration, about half of the above mentioned water in-take can be adsorb- sustained and it can be discharged to outside the body, and at the same time, the guanidino compounds that are accumulated in the body can be decreased, and also the potassium ions can be adsorb- sustained and they can be discharged to outside the body too.

[0036]

Of course, since we know that the above mentioned effective component itself has

been suggested to be used as the digestive ulcer treating agent or as a bleeding control agent, etc., it does not have toxicity, practically, and it is safe even if it is applied in a living body, and even if it is administered orally as in this invention, it will not be absorbed into the internal body, practically, so that its safety is secured.

[0037]

Thus, if the drug for decreasing the guanidino compounds of this invention is utilized, the water control of the above mentioned hemodialysis patient can be made easy, and also, the time required for hemodialysis can be shortened; so that the physical and psychological pain of the patient that accompanies hemodialysis can be reduced.

[0038]

[Actual Examples]

Next, in order to further explain this invention, the methods to produce the water absorbent resin that is utilized as the effective component of this invention will be listed, and then, a prescription example of the drug for decreasing the guanidino compounds of this invention, and the test examples that used this drug, will be explained.

[0039]

[Production Example 1]

Production of sodium poly acrylate cross linked material

1600 mL of cyclo hexane and 16.32 g of sorbitan mono stearate were put into a 5000 mL flask with 4 openings equipped with a mixer, a reflux condenser, a dropping funnel and a pipe for introducing nitrogen gas. While blowing the nitrogen gas into the flask to

remove the oxygen that was dissolved, the temperature was increased to 75 °C.

[0040]

In a separate flask, 510 g of 80 % acrylic acid was added while cooling from the outside, and 544 g of a 30 % aqueous NaOH solution was added to neutralize it, and then, 1.62 g of potassium per sulfate was dissolved. Thereafter, nitrogen gas was blown- in to remove the oxygen that was dissolved in the aqueous solution.

[0041]

The contents of the flask were dropped into the above mentioned flask with 4 openings over a period of 1 hour, and the polymerization reaction was performed. The cyclo hexane was distilled out under reduced pressure, and the remaining swelled polymer was dried at 80 to 100 °C under reduced pressure. By using 300 mL of cyclo hexane, the cross linked polymer that was recovered was washed twice, and the sorbitan mono stearate was removed.

[0042]

Thus, the polymer of which the physiological saline solution absorbing ability per 1 g of cross linked polymer was 53 g, was obtained. From now on, this will be called " polymer A ".

[0043]

The same as before, the polymers of which the physiological saline solution absorbing ability per 1 g of cross linked polymer were each 48 g and 58 g, were obtained. These

are called polymer B and polymer C respectively.

[0044]

[Production Example 2]

Production of poly acrylic acid cross linked material

50 g of the sodium poly acrylate obtained in Production Example 1, was added into 15 L of an aqueous solution of 77.5 g hydrochloric acid while stirring, and this was left for 2 days, and the sodium ions were replaced by hydrogen ions. The obtained polymer was filtered and recovered, and it was washed with de-ionized water, and thereafter, it was added into 3 L of de- ionized water and it was made into a slurry. The water and hydrochloric acid were distilled out from this slurry, and the dried polymer was obtained. This is called polymer D.

[0045]

The Na content in the obtained polymer was 530 ppm; 99 % or more of the sodium acrylate in the polymer was converted into acrylic acid.

[0046]

The physiological saline solution absorbing ability of this material was 1 g.

[0047]

[Production Example 3]

Production of calcium poly acrylate cross linked material

100 g of the sodium poly acrylate obtained in Production Example 1, was put into 5 L of

de- ionized water, and it was swelled. While stirring this, 2.4 L of a 0.2 M aqueous calcium chloride solution was dropped into it, and the desired polymer was obtained. This is called polymer E.

[0048]

In the said polymer, 90 % or more of the sodium acrylate in the raw material polymer was converted into calcium acrylate. The physiological saline solution absorbing ability of this was 18.5 g.

[0049]

[Production Example 4]

Production of sodium poly methacrylate cross linked material

The desired polymer was obtained in the same way as in Production Example 1, except that 714 g of 70 % methacrylic acid was used instead of 80 % acrylic acid, and that it was neutralized by 544 g of a 30 % aqueous NaOH solution while cooling, and then, 0.04 g of methylene bis acryl amide (cross linking agent) and 1.63 g of potassium per sulfate were dissolved, and thereafter, nitrogen gas was blown in and the oxygen that was dissolved in the aqueous solution was removed. This is called polymer F from now on.

[0050]

The physiological saline solution absorbing ability of this material was 47 g.

[0051]

[Production Example 5]

Production of poly methacrylic acid cross linked material

The desired polymer was obtained in the same way as in Production Example 2, except that 55 g of the sodium poly methacrylate cross linked material obtained in Production Example 4 was used instead of the sodium poly acrylate cross linked material. This is called polymer G.

[0052]

The physiological saline solution absorbing ability of this material was 31 g.

[0053]

[Production Example 6]

Production of calcium poly methacrylate cross linked material

The desired polymer was obtained in the same way as in Production Example 3, except that 110 g of the sodium poly methacrylate cross linked material obtained in Production Example 4 was used instead of the sodium poly acrylate cross linked material. This is called polymer H.

[0054]

The physiological saline solution absorbing ability of this material was 20 g.

[0055]

[Production Example 7]

Production of sodium + calcium poly acrylate cross linked material (Na / Ca = 3 / 1)

The desired polymer was obtained in the same way as in Production Example 1, except that it was neutralized by using 408 g of a 30 % aqueous NaOH solution instead of using 544 g of 30 % aqueous NaOH solution, and also that the neutralization was performed by using the suspension liquid which consisted of 126 g of $Ca(OH)_2$ and 150 g of de- ionized water. This is polymer I.

[0056]

The calcium substitution degree of this material was 25 %, and the physiological saline solution absorbing ability of this material was 43 g.

[0057]

[Prescription Example 1]

Production of capsule agent

As the effective component, the self cross linked material of sodium poly acrylate obtained in Production Example 1 (neutralization degree : 72 %, water absorbing ability : 53 g, polymer A.) was filled into an orally administered gelatin capsule of the desired size, and 1000 hard gelatin capsules which contained 250 mg per capsule, were prepared.

[0058]

[Prescription Example 2]

Production of capsule agent

As the effective component, polymer A and the self cross linked material of calcium poly acrylate obtained in Production Example 3 (neutralization degree : 70 %, water absorbing ability : 18.5, polymer B (this might be a typo of polymer E, Translator)) were uniformly mixed and it was filled into an orally administered gelatin capsule of the desired size, and 1000 hard gelatin capsules which contained 150 mg of polymer A and 150 mg of polymer B (*typo of E?, Translator*) per capsule, were prepared.

[0059]

[Pharmacological Test Example 1]

SD type male rats, 7 weeks old, (a product of Nihon Charles River Co.) were separated into 6 - 8 rats per group. After they were grouped, the kidneys were totally removed from all the rats in the afternoon of the first day. Namely, the rat was put under anesthesia by Nembutal, and the hair on both the back and sides were shaved, and the abdominal wall was cut open at the lower end of the ribs. The kidneys that were wrapped with fat tissue were pulled out, and the renal artery, the renal vein and the urine tube were tied up, and thereafter, the kidney was cut off, and the incisioned part of the abdominal wall and skin were sutured together.

[0060]

As the drug to be tested, polymer A was suspended in the commercially sold "shiso?" oil, and an administering liquid with a concentration of 300 mg / mL was prepared. The administered amount at each time was decided to be 1 mL. The administration was

done for a total of 5 times, at 8 PM of the first day, 8 AM, 2 PM and 8 PM of the second day, and 8 AM of the third day. 10 mL of water and then 1 mL of the suspension liquid of the above mentioned drug to be tested were orally administered by using a gastric tube. After the last administration, each rat was killed, and the blood was collected and it was dissected. (Experimental group).

[0061]

As the control group, a group was provided to which 10 mL of water and 1 mL of only "shiso?" oil which did not contain the drug was administered instead of the suspension liquid of the above mentioned drug.

[0062]

In addition, as the reference group, a group of normal rats (rats which did not go under the kidney removal operation) was provided which were allowed to take water freely, and to which 1 mL of only "shiso?" oil which did not contain the drug was administered instead of the suspension liquid of the above mentioned drug.

[0063]

During the period of the experiments, the rats of each group could eat food freely, however, their water intake was only the load given the above mentioned oral administration.

[0064]

In the above mentioned experiment, the body weights of each group of rats were measured before the experiment (prior to the administration of the suspension liquid),

and after the experiment was completed (after the last administration at 2 PM on the third day and before dissection). Also, the water content in the body was measured by the following method.

[0065]

Namely, after the experiment was completed, each rat was killed and its blood was collected, and then, the internal organs, fat and digestive tubes were cut off, and the rat weight was measured. (This is mostly consists of bone, muscle and skin. From now on, this will be called the "weight before drying"). Thereafter, it was dried at 70 °C for 1 week, and this weight was measured (this is called the "dried weight"). The value obtained by subtracting the "dried weight" from the above mentioned "weight before drying" is considered to be the water accumulated in the body, and the value where the accumulated water was divided by the "weight before drying" was obtained as the water content proportion in the body.

[0066]

Also, the blood (serum) that was collected, was measured for its serum sodium, potassium, and chlorine ion concentrations.

[0067]

Each measured value was disperse- analyzed, and thereafter, it was statistically handled by the Dunnett - Two Tail method, and it was examined.

[0068]

The obtained results (average ± S. E.) are shown in Figure 1 (fluctuation of the body weight), in Figure 2 (water content proportion in the body), and in Table 1 (serum sodium, potassium and chlorine ion concentration).

[0069]

In each figure, (1) indicates the control group (n = 8), and (2) indicates the experimental group to which the test drug was given at 300 mg each time (n = 7), and (3) indicates the reference group (n = 6). In the figure, the black star marks indicate $p < 0.01$ vs. the control group (1) by the above mentioned statistical treatment.

[0070]

[Table 1]

Group	Na^+ (mEq / l)	K^- (mEq / l)	Cl^- (mEq / l)
(1)	116.492 ± 0.972	9.657 ± 0.806	75.571 ± 1.270
(2)	140.857 ± 1.471 **	6.071 ± 0.253 **	82.857 ± 1.408 **
(3)	141.500 ± 0.619 **	5.400 ± 0.190 **	101.167 ± 0.749 **

** indicates $p < 0.01$ vs. the control group (1).

[0071]

The following things are clear from the above mentioned results.

[0072]

Namely, from Figure 1, we can see that the control group (1) showed an average of about 30 g of weight increase, however, the weight increase of the experimental group (2) into which the drug of this invention was administered at 300 mg/ each time, was about 10 g, and this is about equal to the weight increase of the reference group (3).

[0073]

According to Figure 2, the water content proportion in the bodies of the experimental group (2) into which the drug of this invention was administered at 300 mg / each time, averaged 0.691, compared with that of the control group (1) which averaged 0.709, and it is clear that the accumulation of water in the body was restricted significantly ($p < 0.01$) compared with the control group.

[0074]

According to Table 1, the serum potassium concentration showed a significantly higher value when the kidney was removed compared with the normal rats. On the other hand, the serum sodium and chlorine concentrations show significantly lower values. (Comparison of Reference group (3) and the control group (1).)

[0075]

However, the experimental group (2) into which the drug of this invention was administered at 300 mg / each time, can clearly restrict the obvious increase in the serum potassium concentration and the decrease in the serum sodium which are seen in the above mentioned control group (1).

[0076]

[Pharmacological Test Example 2]

8 Wister type male rats, 8 weeks old, (a product of Nihon Charles River Co.) were used for 1 group. (They were grouped based on the weight of each rat.) After they were grouped, the kidneys were totally removed from all the rats on the afternoon of the first day. Namely, the rat was put under anesthesia by Nembutal, and the hair on both the back and sides were shaved, and the abdominal wall was cut open at the lower end of the ribs. The kidneys that were wrapped with fat tissue were pulled out, and the renal artery, the renal vein and the urine tube were tied up, and thereafter, the kidney was cut off, and the incisioned part of the abdominal wall and skin were sutured together.

[0077]

As the drug to be tested, each of sodium poly acrylate (food additive grade, made by Wako K.K., from now on this will be called "polymer J"), polymer B, polymer C, polymer D and polymer E were suspended in the commercially sold "shiso?" oil, and administering liquids with concentrations of 250 mg / mL and 100 mg / mL were prepared. The administered amount at each time was decided to be 1 mL. The administration was done for a total of 3 times at 9 PM of the first day, 9 AM of the second day, and 9 PM of the second day. 15 mL of water and then 1 mL of the suspension liquid of the above mentioned drug to be tested were orally administered by using a gastric tube. After the last administration, each rat was killed, and the blood was collected, and it was dissected. (Experimental group).

[0078]

As the control group, a group was provided to which 15 mL of water and 1 mL of only "shiso?" oil which did not contain the drug was administered instead of the suspension liquid of the above mentioned drug.

[0079]

In addition, as the reference group, the rats were provided of which the abdominal wall was cut open but the incisioned parts were sutured together without removing the kidney instead of under going the kidney removal operation, and the water intake was restricted in one group (Reference group I), and the other group could intake water freely (Reference group II).

[0080]

During the period of the experiments, the rats of each group could eat food freely,

however, their water intake was only the load given by the above mentioned oral administration.

[0081]

In the above mentioned experiment, the body weights of each group of rats were measured before the experiment (prior to the administering the suspension liquid), and after the experiment was completed (9 AM on the third day and before dissection). Also, the water content proportion in the body was measured by the following method.

[0082]

Namely, after the experiment was completed, each rat was killed and its blood was collected, and then the internal organs, fat and digestive tubes were cut off, and the rat weight was measured. (This is mostly consists of bone, muscle and skin. From now on, this will be called the "weight before drying"). Thereafter, it was dried at 70 °C for 1 week, and this weight was measured (this is called the "dried weight"). The value obtained by subtracting the "dried weight" from the above mentioned "weight before drying" is considered to be the water accumulated in the body, and the value where the accumulated water was divided by the "weight before drying" was obtained as the water content proportion in the body.

[0083]

Also, the blood (serum) that was collected, was measured for its serum sodium, potassium, chlorine and magnesium ion concentrations.

[0084]

Concerning the blood plasma, the guanidino compounds that were separated by a strongly acidic cation exchange resin, were reacted with ninhydrin under alkaline conditions, and the strength of the flourescent light obtained, was measured, and thus, each guanidino compound was quantified [Hiraga, Y. et al., J. Chematography, 226, 43- 51 (1981) ; Sasaki et al., Nihon Rinsho, 47, 1989 special edition, 397 - 401 (1989)].

[0085]

Each measured value was disperse- analyzed, and thereafter, it was statistically handled by the Dunnett - Two Tail method, and it was examined.

[0086]

The results obtained (average ± S. E.) are shown in Figure 3 (change in the body weight), in Figure 4 (water content proportion in the body), in Table 2 (serum potassium and magnesium ion concentration), and in Figure 5 (concentration of guanidino compounds in the blood).

[0087]

In each figure and the table, (1) indicates the Reference group I, (2) indicates the Reference group II, (3) indicates the control group, (4) indicates the experimental group in which polymer J was administered, (5) indicates the experimental group in which polymer B was administered, (6) indicates the experimental group in which

polymer C was administered, (7) indicates the experimental group in which polymer E was administered, and (8) indicates the experimental group in which polymer D was administered.

[0088]

In Figure 3 and Figure 5, the white bar graph in each experimental group indicates the case of administering the drug at 100 mg / mL, and the black bar graph indicates the results when the drug was administered at 250 mg / mL.

[0089]

The star marks indicate a $p < 0.05$ vs. the control group (3) by the statistical treatment.

[0090]

[Table 2]

Group	K^- (mEq / l)
(1)	6.18 ± 0.57
(2)	6.63 ± 0.21 *
(3)	8.79 ± 1.77
(4)	7.16 ± 0.98
(5)	6.79 ± 0.87 *
(6)	6.31 ± 1.00 *

* mark indicates the $p < 0.05$ vs. the control group (3).

[0091]

The following things are clear from the above mentioned results.

[0092]

Namely, from Figure 3, we can see that the weight increase in the experimental groups (4), (5) and (6) into which the drug of this invention was administered at 250 mg, were about 10 to 15 g compared with the control group (3) in which an average of about 25 g of weight increase was recognized, and a statistically significant ($p < 0.05$) difference compared with the control group (3) was seen.

[0093]

According to Figure 4, the water content proportion in the body of the experimental groups (4), (5), (6) and (8) into which the drug of this invention was administered at

250 mg, were significant compared with that of the control group (3) which averaged 0.710, therefore it is clear that the accumulation of water in the body was restricted significantly ($p < 0.05$) compared with the control group (3). Concerning the experimental group (7) into which polymer E was administered, it is clear that the accumulation of water in the body tends to be restricted, although a statistically significant difference was not recognized.

[0094]

According to Table 2, when the kidney was removed, the serum potassium ion concentration showed a higher value (see the control group) compared with the normal rat (reference group). Compared with this, the obvious increase in the serum potassium ions that could be recognized in the above mentioned control group, was not able to be recognized in the experimental groups (4), (5) and (6) into which the drug of this invention was administered at 250 mg / mL, and we can see that it indicates a significantly ($p < 0.05$) lower value, and that the increase in the potassium ion concentration can be obviously restricted.

[0095]

In addition, according to Figure 5, the concentrations of guanidino compounds (guanidino butyric acid (GBA), guanidino propionic acid (GPA) and methyl guanidino (MG)) are all lower than the detection limit value in Reference group I and Reference group II, however, the concentration of these guanidino compounds clearly increases by conducting the operation of total kidney removal, and they accumulate in the blood (See control group (3)).

[0096]

However, it is clear that the obvious increase in the concentration of guanidino compounds in the blood (accumulation in blood) that could be seen in the above mentioned control group (3) could be restricted in the experimental groups (4), (5), (6), (7) and (8) into which the drug of this invention was administered at 250 mg.

[Simple Explanation of the Figures]

[Figure 1]

This is a graph which indicates the change in the body weight of the animals that were tested, which was measured according to Pharmacological test example 1.

[Figure 2]

This is a graph which indicates the water content proportion in the bodies of the animals that were tested, which was measured according to Pharmacological test example 1.

[Figure 3]

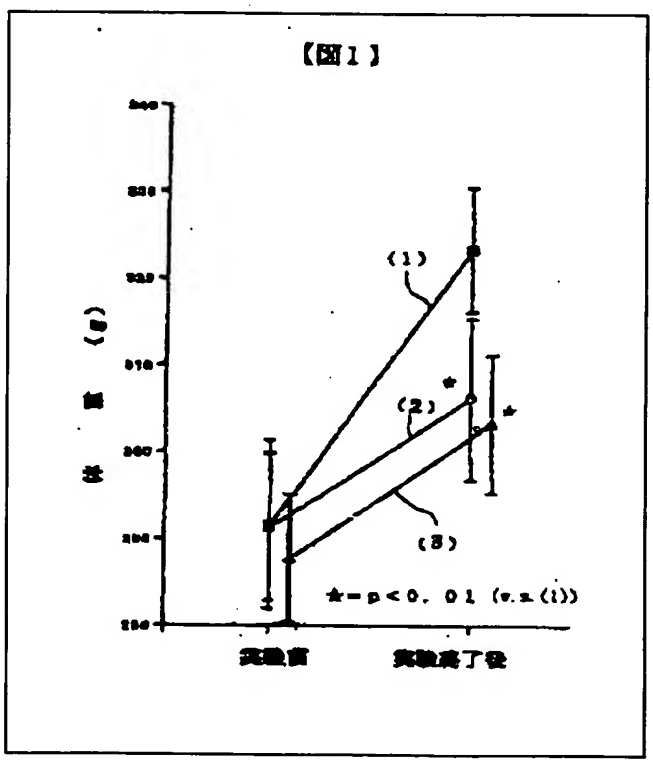
This is a graph which indicates the change in the body weights of the animals that were tested, which was measured according to Pharmacological test example 2.

[Figure 4]

This is a graph which indicates the water content proportion in the bodies of the animals that were tested, which was measured according to Pharmacological test example 2.

[Figure 5]

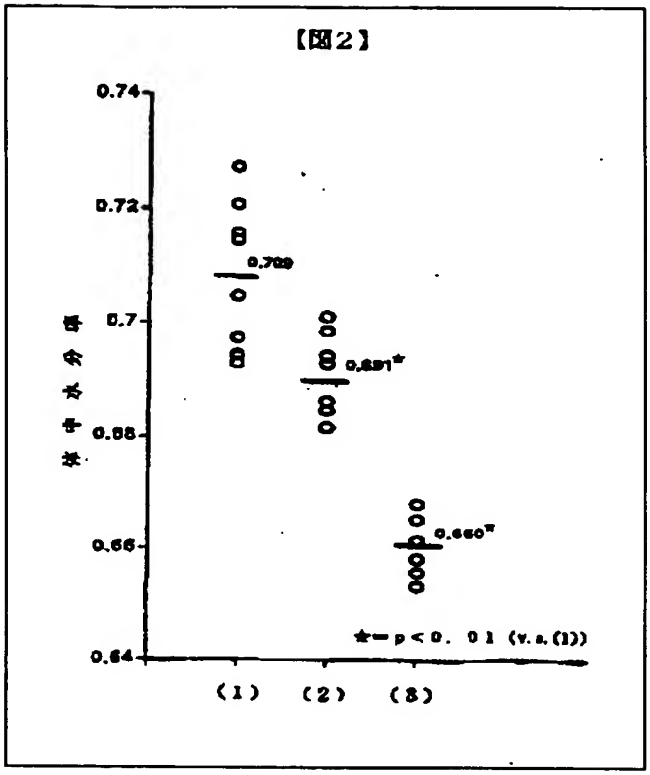
This is a graph which indicates the concentration of guanidino compounds in the blood of the animals that were tested, which was measured according to Pharmacological test example 2.



The Y axis is the "body weight".

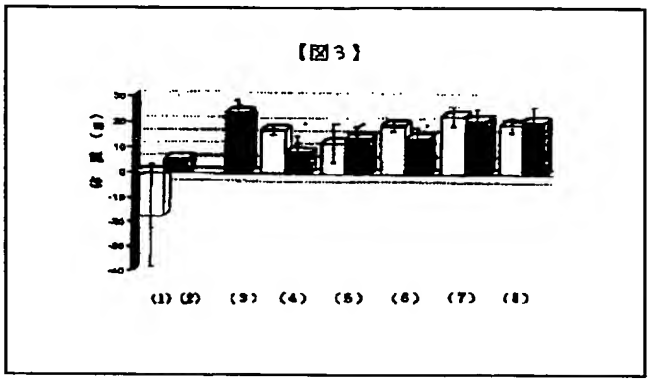
On the X axis, the word on the left is "before experiment", and the word on the right is "After completion of the experiment".

【図2】

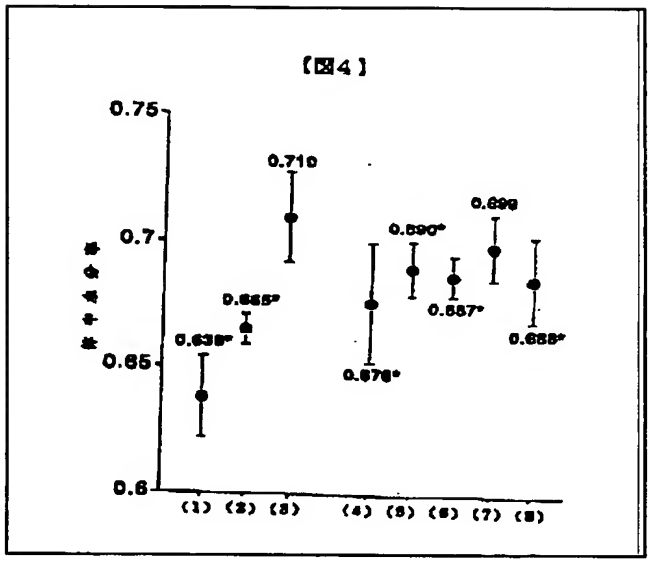


The Y axis is the “water content proportion”.

【図3】

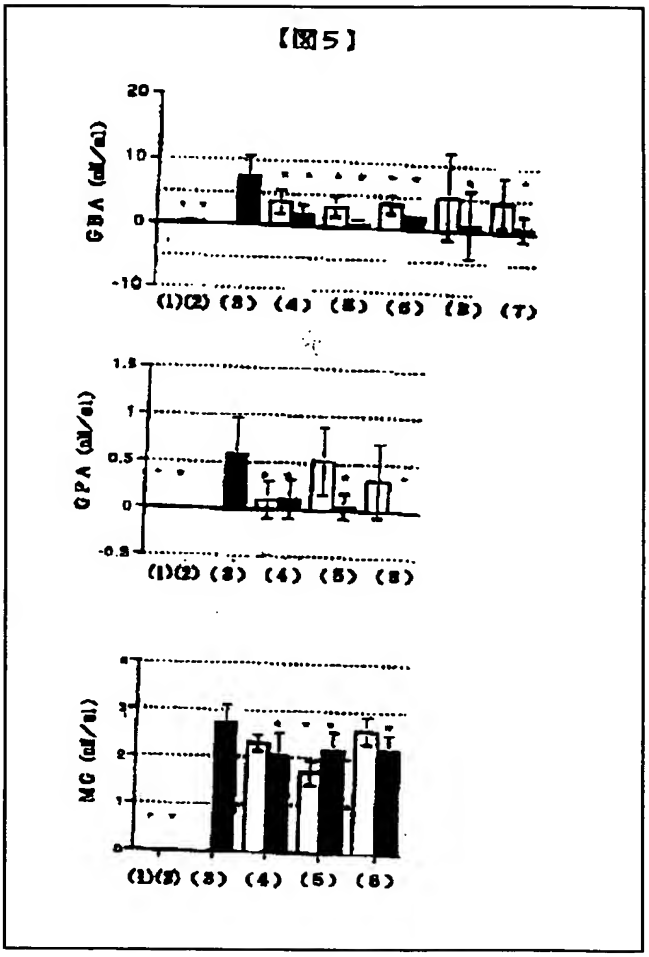


The Y axis is the “body weight” (g).



The Y axis is the “water content proportion”.

【図5】



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L10 ANSWER 1 OF 1 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1998-212711 [19] WPIDS
DNN N1998-169094 DNC C1998-067210
TI Guanidino compound-lowering agent - comprises hydrophilic acrylic resin, for water and potassium ion adsorbent.
DC A14 B04 P34
PA (KAOS) KAO CORP; (SAKA) OTSUKA SEIYAKU KOGYO KK
CYC 1
PI JP--10059851 A 19980303 (199819)* 9p A61K-031-78 <--
ADT JP--10059851 A 1996JP-0256387 19960927
PRAI 1996JP-0149072 19960611
IC ICM A61K-031-78
ICA A61M-001-14; A61M-001-36
AB JP 10059851 A UPAB: 19980512
Guanidino cpd.-lowering agent comprising a hydrophilic acrylic resin is new.

Also claimed are: a guanidino cpd.-lowering agent and water adsorbent contg. a hydrophilic acrylic resin; and a guanidino cpd.-lowering agent and water and potassium ion adsorbent contg. a hydrophilic acrylic resin (but not potassium salt).

ADVANTAGE - Guanidino cpds., water and potassium ions accumulated in the body of a patient receiving haemodialysis are excreted by oral admin. of this agent. The time taken for haemodialysis is reduced by the use of this agent.

Dwg.0/5
FS CPI GMPI
FA AB; DCN
MC CPI: A04-F04; A12-V01; B04-C03B